



Metastasectomy in Stage IV Melanoma: How and When Should We Employ It?

Mark B. Faries, MD, FACS^{1,2} , and Michael Lowe, MD, FACS³

¹Surgery, Cedars-Sinai Medical Center, Los Angeles, CA; ²Surgical Oncology, The Angeles Clinic and Research Institute, Los Angeles, CA; ³Department of Surgery, Emory University School of Medicine, Atlanta, GA

Nancy was first diagnosed with melanoma in 1971 at the age of 23. She did well until about 10 years later when, during a pregnancy, she noted an enlarged cervical lymph node that proved to be a nodal metastasis, which was cleared through a neck dissection. Then in 2009 a screening mammography showed a right breast mass that turned out to be metastatic melanoma. Concomitant complete imaging showed disease in her right lung and in a deep gluteal lymph node. With a paucity of good systemic treatment options, these were all resected. A year and a half later she had two small bowel metastases resected, then a kidney metastasis 18 months after that. Then a gluteal soft tissue metastasis was resected a year later and an omental metastasis several months after that. Then in 2015, for no apparent reason the metastases stopped coming, and as of this month they have yet to reappear. Throughout she has never received a checkpoint blocking antibody or targeted small molecule inhibitor. Her metastatic history predates the availability of those options, and at the age of 75, she is not particularly interested in trying them now. Metastatic melanoma can be a peculiar disease.

Although admittedly an anecdote, Nancy's "surgery-only" treatment was not unusual in the era that preceded the development of today's effective systemic therapies. Reported long-term survival in metastasectomy series was typically 20–30% and as high as 45% in one clinical trial that enrolled patients with resected stage IV.^{1–3} These outcomes were markedly better than those of patients treated without

surgery at the time, although there is no very reliable way to account for surgical selection bias on the basis of patient fitness and disease biology. Reports at the time identified factors that were associated with prolonged survival after resection including solitary lesions, tumors with slower growth rates, the absence of prior stage III disease, normal lactate dehydrogenase, and complete resection.^{1,3,4} However, these were prognostic factors rather than predictive markers that might have been specifically associated with benefit from surgery. Quantification of any benefit specifically attributable to resection remained elusive, but surgery was preferred by many, due to the lack of alternatives.

The world has changed, though, with the development of effective targeted and checkpoint blockade drugs. The most aggressive current systemic therapy regimens report long-term overall survival of over 50% beyond 5 years, which raises the question of whether surgery still has an important role for patients with metastatic melanoma in the modern therapeutic environment.⁵ The current report from Lwin and colleagues provides information about just that issue.⁶ They examined the National Cancer Database (NCDB) for patients with stage IV melanoma between 2012 and 2017, when modern therapies would have been available, and found that about one in five of these patients had surgical treatment. In the absence of immunotherapy, patients who underwent surgery had substantially better survival than those who did not. Importantly, patients receiving both immunotherapy and resection had better outcomes than those who only received immunotherapy. Similar observations have been made after other multivariable examinations of the NCDB and in institutional series using both multivariable and matched-pair strategies to control for confounding variables.^{7,8} To our knowledge, the highest reported overall survival for any trial in stage IV melanoma is in the IMMUNED study, in which patients receiving CTLA-4 and PD-1 blockade after resection of stage IV melanoma was more than 80% at 5 years.⁹

© Society of Surgical Oncology 2023

First Received: 19 April 2023

Accepted: 4 June 2023

Published online: 16 June 2023

M. B. Faries, MD, FACS

e-mail: mfaries@theangelesclinic.org

Thus the evidence for surgical benefit appears as strong in the modern era as it did in earlier times. Why, then, is metastasectomy only an option for resectable stage IV melanoma in current guidelines, rather than the favored approach?¹⁰ The lack of prospective, randomized trial data demonstrating benefit is almost certainly the reason. This gap means it is not possible to accurately determine which patients are best served by resection and which should avoid the operating room. Another observation Lwin and colleagues make is that our current selection of patients for surgical therapy appears based, at least in part, on economic or environmental factors, rather than tumor or patient characteristics. Two of the biggest selection factors appear to be private insurance and treatment at an academic center, which confirms prior reports.⁷ These variables are unlikely to have anything to do with who intrinsically or biologically benefits from metastasectomy. It implies that these factors impact the willingness of the treatment team to even consider surgical resection.

The absence of high-level data is not entirely for lack of effort. In 2009, a trial randomizing patients with resectable stage IV melanoma to either metastasectomy or investigator's choice of medical therapy (no drug was proven to be better than placebo at that point) was opened at 19 centers around the world (NCT01013623). Over 3 years, only 12 patients were enrolled, and the trial was never completed. At the time there were those who felt uneasy randomizing patients who could be resected to a medical therapy. In the current therapeutic era, that sentiment is certainly reversed in many places.

So is it too late to find an answer to the difficult question of who benefits from metastasectomy in stage IV melanoma? We would assert that it is indeed possible and that we are obligated to do our best to get to a definitive resolution. This would require a prospective clinical trial randomizing patients to treatment with or without metastasectomy. With the apparent success of the neoadjuvant approach in stage III melanoma, it may be sensible to use the neoadjuvant paradigm for the surgical arm. Patients would receive an initial brief period of systemic therapy, followed by either resection or continued systemic therapy alone. Which systemic therapy to choose? Dictating a single regimen may not be possible, but an acceptable, limited number of therapies using a PD-1 blockade backbone may be feasible. What endpoint to choose? Melanoma-specific survival would be a gold standard, but in this advanced disease setting alternatives such as progression-free survival could be entertained, which might allow for the possibility of crossover. Data derived from such a trial may also create opportunities to subsequently examine other important clinical questions such as de-escalation of either surgery or systemic therapy

based on pathologic response assessed at the time of resection. Given the tremendous progress in systemic therapy, it is clear whether almost all patients with stage IV melanoma should receive systemic therapy if possible. It is also very likely that some of these patients will derive very meaningful benefit from metastasectomy as well. We need to do our best to enable as many patients as possible to, like Nancy, move past their encounters with metastatic melanoma to a future free of disease.

DISCLOSURES Mark Faries serves on the advisory boards of Merck, Bristol-Myers Squibb, Regeneron, and Instil Bio.

REFERENCES

1. Wankhede D, Grover S. Outcomes after curative metastasectomy for patients with malignant melanoma: a systematic review and meta-analysis. *Ann Surg Oncol.* 2022;29:3709–23.
2. Sosman JA, Moon J, Tuthill RJ, et al. A phase 2 trial of complete resection for stage IV melanoma: results of Southwest Oncology Group Clinical Trial S9430. *Cancer.* 2011;117(20):4740–6.
3. Faries MB, Mozzillo N, Kashani-Sabet M, et al. Long-term survival after complete surgical resection and adjuvant immunotherapy for distant melanoma metastases. *Ann Surg Oncol.* 2017;24:3991–4000.
4. Ollila DW. Complete metastasectomy in patients with stage IV metastatic melanoma. *Lancet Oncol.* 2006;7:919–24.
5. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. *J Clin Oncol.* 2022;40:127–37.
6. Lwin T, Kaelberer Z, Ruan M, et al. Surgical utilization and outcomes for patients with stage IV melanoma in the modern immunotherapy era. *Ann Surg Oncol.* (2023). <https://doi.org/10.1245/s10434-023-13543-y>.
7. Elias ML, Behbahani S, Maddukuri S, et al. Prolonged overall survival following metastasectomy in stage IV melanoma. *J Eur Acad Dermatol Venereol.* 2019;33:1719–25.
8. Nelson DW, Fischer TD, Graff-Baker AN, et al. Impact of effective systemic therapy on metastasectomy in stage IV melanoma: a matched-pair analysis. *Ann Surg Oncol.* 2019;26:4610–8.
9. Livingstone E, Zimmer L, Hassel JC, et al. Adjuvant nivolumab plus ipilimumab or nivolumab alone versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): final results of a randomised, double-blind, phase 2 trial. *Lancet.* 2022;400:1117–29.
10. Swetter SM, Thompson JA, Albertini MR, et al. NCCN guidelines(R) insights: melanoma: cutaneous, version 2.2021. *J Natl Compr Canc Netw.* 2021;19:364–76.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.